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The Risk of Pancreatic Cancer Following Pancreatitis: An Association Due to Confounding?

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Background & Aims: **Chronic pancreatitis has been suggested as a causal risk factor for pancreatic cancer in a recent study. The aim of this study was to clarify the relationship between chronic pancreatitis and pancreatic cancer.** ***Methods:*** **All patients in the Swedish Inpatient Register with a discharge diagnosis of pancreatitis from 1965 to 1983 were identified. They were stratified into subcohorts as follows: (1) one episode of unspecified pancreatitis (n = 823); (2) one episode of acute pancreatitis (n = 24,753); (3) recurrent pancreatitis (n = 7328); and (4) chronic pancreatitis (n = 4546). We also identified those with associated diagnoses indicating gallbladder disease or alcoholism. The patients were followed up through record linkage to the nationwide Swedish Cancer Register, Death Register, and Migration Register.** ***Results:*** **After exclusion of cancers occurring in the first year, there were excess risks for pancreatic cancer in all subcohorts. However, the risks declined with time in all subcohorts. A persistent excess risk after 10 years was restricted to patients with associated alcohol abuse (standardized incidence ratio, 3.8; 95% confidence interval, 1.5–7.9).** ***Conclusions:*** **The findings are not consistent with reports that pancreatitis is causally associated with a long-term risk of pancreatic cancer. Selection bias, alcohol consumption, and smoking may contribute to some of the patterns of risk that have been observed.**

Little is known of the etiology of exocrine pancreatic cancer. Presently, there are no generally accepted risk factors other than smoking and diabetes.[1-9] Recently, Lowenfels et al.[10] reported a 16-fold increased risk for pancreatic cancer in a multicenter study of patients with chronic pancreatitis. The excess risk remained unchanged even 10 years or more after the diagnosis. If true, such an association could provide important clues to the etiology of this cancer. However, concerns have been raised regarding the magnitude of the reported association and the methodology.[11] The risks of pancreatic cancer were much lower in a Swedish cohort study of all patients discharged with a diagnosis of pancreatitis in the Uppsala Health Care Region[12] and in a recent cohort study from the United States.[13] In the Swedish study, the incidence of pancreatic cancer did not differ from that expected 10 years or more after the first discharge for pancreatitis, but low statistical power prevented meaningful analysis of patient subgroups.

To evaluate further the possible association between different forms of pancreatitis and pancreatic cancer, we used the nationwide Inpatient Register in Sweden to identify a large cohort that permitted analyses of subgroups with a follow-up duration of up to 25 years. This report is an expansion of our earlier study.[12]

Materials and Methods

The Cohort

Beginning in 1965, the National Board of Health and Welfare started collecting data on individual hospital discharges in the Inpatient Register. The registration expanded steadily to cover 85% of the Swedish population in 1983. Each record contains up to eight discharge diagnoses, coded according to the seventh revision of the International Classification of Diseases (ICD-7) through 1967 and the eighth revision (ICD-8) thereafter. The patients were identified through their national registration numbers (NRNs), which are unique for every Swedish resident.[14] The register is almost complete.[15] The codes for the main diagnoses are judged to be correct at the detailed five-digit level in 83%–86% of the records.[16] Because there is almost no private inpatient treatment in Sweden, with patients obliged to use the public hospitals in the county where they live, the Inpatient Register is essentially population based and referable to the population of the counties covered by the registration.

We first selected all records in the register with a diagnosis of acute, chronic, or unspecified pancreatitis. Cross-linkage within the register identified the first discharge (index hospitalization) with these diagnoses for each unique NRN. There

Abbreviations used in this paper: **CI, confidence interval; ICD, International Classification of Diseases; NRN, national registration number; SIR, standardized incidence ratio.**

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were 38,175 unique NRNs with one or more records that contained the specified diagnostic codes. NRNs that could not be found in the Register of the Total Population, Migration Register, or Death Register held by Statistics Sweden were judged to have been incorrectly entered. Records with such NRNs (n = 5335; 14.0%) were excluded because they were not available for follow-up. We also excluded 3310 (8.7%) records in which inconsistencies (e.g., death before discharge, or different sex codes for the same NRN) were disclosed during the linkage procedures. By record linkage to the Cancer Register, established in 1958 and virtually complete,[17–19] we excluded patients with prevalent pancreatic cancers and patients with cancers diagnosed at the index hospitalization.

A total of 29,530 patients were included in the cohort, with characteristics shown in Table 1. The patients were allocated to the following subcohorts, effective from the date when their respective diagnosis first occurred: (1) one discharge with unspecified pancreatitis (ICD-7, 587.21–587.23, 587.28; ICD-8, 577.09, 577.91–577.93, 577.98); (2) one discharge with diagnoses of acute pancreatitis (ICD-7, 587.00–587.02, 587.09; ICD-8, 577.00–577.02, 577.08); (3) two or more discharges with diagnoses of acute or unspecified pancreatitis; and (4) one or more discharges with chronic pancreatitis (ICD-7, 587.10, 587.19–587.20; ICD-8, 577.10, 577.19, 577.90). Thus, all patients in subcohort 3 contribute person-years in subcohort 1 or 2 until the date of their second discharge with a diagnosis of acute or unspecified pancreatitis. However, once a patient was included in subcohort 4, he or she remained there regardless of any subsequent diagnoses. Table 2 shows more details about the subcohorts.

We also identified the 4746 male and 6232 female patients in the cohort with concurrent or subsequent diagnosis of gallbladder disease (ICD-7, 584.00–585.19; ICD-8, 574.00–575.03) and the 3569 male and 474 female patients with alcoholism (ICD-7, 307.00–307.99, 322.00–323.99, 581.10, 583.10; ICD-8, 291.00–291.99, 303.00–303.99, 571.00–571.01) (Table 1). Pancreatitis patients with alcoholism were younger than those with gallstones (mean age, 46.2 and 61.8 years, respectively, for men, and 46.6 and 58.0, respectively, for women), whereas men with multiple acute or chronic pancreatitis were younger than those with only one acute episode of pancreatitis (mean ages, 50.5, 51.9, and 55.0 years) (Table 2).

Table 1. Characteristics of the Original Cohort

	Men	Women	Total
No. of patients	17,664	11,866	29,530
Mean (median) age at entry into cohort (*yr*)	53.4 (50)	56.3 (55)	54.5 (50)
No. of persons observed by follow-up time (*yr*)			
1–4	16,563	11,257	27,820
5–9	14,595	10,276	24,871
10–24	9438	7243	16,681
No. of persons accrued by age groups at time of entry (*yr*)			
<30	1506	1406	2912
30–39	3142	1468	4610
40–49	3499	1523	5022
50–59	3613	2140	5753
60–69	3130	2350	5480
70–79	2120	2094	4214
80+	654	885	1,539
Alcoholism diagnosis			
No. of persons	3569	474	4043
Mean age at entry (*yr*)	46.2	46.6	46.2
Gallbladder disease			
No. of persons	4746	6232	10,978
Mean age at entry (*yr*)	61.8	58.0	59.7
No. of observed pancreatic cancers	135	107	242
Mean age at cancer diagnosis (*yr*)	66.3	67.9	66.9

Follow-up

Record linkage to the Swedish Cancer Register identified all cases of cancer. The Death Register provided information on date and cause of death among those who died. Both the registers are considered to be almost complete, with an underreporting <4%.[17–19] Date of emigration, when applicable, was established in the Migration Register. The time of observation was calculated from the date of the discharge rendering admittance to the subcohort until the occurrence of a pancreatic cancer, death, emigration, transfer to other subcohort, or the end of the observation period (December 1989), giving a maximum follow-up duration of 25 years.

Statistical Methods

The expected numbers of cancers were calculated by multiplying the observed number of person-years by age- (5-year groups), sex-, and calendar year–specific cancer incidence rates derived from the entire Swedish population. The standardized incidence ratio (SIR), defined as the ratio of observed to expected numbers of cancers, was used as a measure of relative risk. The 95% confidence interval (CI) of the SIR was then calculated on the assumption that the observed numbers follow a Poisson distribution.[20] To avoid possible ascertainment bias related to differential autopsy rates among pancreatitis patients and the general population, we excluded cancers diagnosed incidentally at autopsy from both the observed and expected rates.

Results

We identified 472 patients with a diagnosis of pancreatic cancer subsequent to a pancreatitis diagnosis. To avoid the impact of pancreatic cancers being initially misdiagnosed as pancreatitis, and selection bias resulting from an increased likelihood of being hospitalized for pancreatitis when symptoms of an unrecognized cancer are superimposed, we excluded the first year of follow-up, thus removing 242 patients with pancreatic cancers observed in the first year.

There were 29,530 individuals, 17,664 men and

Table 2. Characteristics of the Subcohorts

	One unspecified pancreatitis	One acute pancreatitis	Multiple pancreatitis	Chronic pancreatitis
No. of patients[a]	823	24,753	7328	4546
Men/women	456/367	14,591/10,162	4961/2367	3282/1264
Mean age at entry into cohort (*yr*)	56.3	54.0	52.5	53.2
Men/women	55.0/58.0	52.7/55.9	50.5/56.6	51.9/56.4
No. of persons observed by follow-up time (*yr*)				
1–4	540	19,494	6312	3831
5–9	409	16,053	5521	3590
10–24	239	10,457	3637	2457
No. of persons accrued in age groups at time of entry (*yr*)				
<30	65	2572	819	352
30–39	97	3933	1485	855
40–49	127	4165	1426	1028
50–59	178	4670	1311	1016
60–69	182	4506	1129	756
70–79	132	3566	846	427
80+	42	1342	312	112
No. of observed pancreatic cancers	30	152	101	189
Mean age at cancer diagnosis (*yr*)	66.4	67.6	66.2	65.2

[a]One patient can, in different time periods, be a member of more than one subgroup.

11,866 women, available for follow-up evaluation 1 year or more after the first discharge for pancreatitis, of whom 230 had a subsequent diagnosis of pancreatic cancer. Excess risks for pancreatic cancer were observed in all subcohorts (Table 3). The SIR for all cohorts combined was 2.8 (95% CI, 2.5–3.2), similar for men and women. The highest risks were observed in the patients with chronic pancreatitis (SIR, 7.6; 95% CI, 6.0–9.7) and with one attack of unspecified pancreatitis (SIR, 7.3; 95% CI, 3.5–13.4). There were no important sex differences in any of the subcohorts, except for higher relative risks among women in the group with one unspecified episode. Stratified analysis by latency time revealed decreasing relative risks with time in all subcohorts. After 10 years or more, the excess risk in the combined cohort declined and was of borderline significance (SIR, 1.5; 95% CI, 1.1–2.0). In the subcohorts, a significantly increased risk after 10 years or more was associated only with recurrent acute or unspecified pancreatitis (SIR, 2.2; 95% CI, 1.2–3.7), whereas the elevated twofold risks among chronic and unspecified pancreatitis patients were statistically nonsignificant.

Separate analyses for patients with a concurrent diagnosis of gallbladder disease, alcoholism, and those without either of these diagnoses revealed differences in risk of pancreatic cancer. 'hose with pancreatitis associated with gallbladder disease had a SIR of 1.9 (95% CI, 1.6–2.4) 1 year or more after the first discharge, but the risk did not differ significantly from that expected 10 years or more after the first pancreatitis diagnosis (SIR, 1.3; 95% CI, 0.8–1.9). In contrast, those with a diagnosis of alcoholism had a significantly increased risk even after 10 years of follow-up (SIR, 3.8; 95% CI, 1.5–7.9). Those without any indication of gallbladder disease or alcoholism had the highest overall risk (SIR, 3.9; 95% CI, 3.3–4.7), but mainly during the first few years. After 10 years, the SIR in this subgroup was only 1.5 (95% CI, 0.8–2.4) (Table 3).

Because smoking may act as a confounder, we analyzed the risk for smoking-related malignancies (e.g., respiratory cancer) for patients with pancreatitis associated with gallbladder disease or alcoholism and for those without these codiagnoses (Table 4). Not surprisingly, patients with alcoholism had a substantially increased risk for respiratory cancer that remained evident 10 years after the first discharge, as opposed to those with gallbladder disease, whose risk did not differ from that in the general population. Patients without gallbladder disease or alcoholism had an increased risk for respiratory cancer after 10 years, but the risk was less prominent than observed after a diagnosis of alcoholism.

Discussion

In a previous study, we found a twofold increased risk for pancreatic cancer arising 2 or more years after the first hospitalization for pancreatitis.[12] The updated results in our expanded cohort are consistent with our earlier findings but not with the 16-fold increased risk

Table 3. Standardized Incidence Ratio for Pancreatic Cancer by Sex and by Years Since Diagnosis of Pancreatitis, and by Presence of Gallbladder Disease and Alcoholism

	1–4 yr			5–9 yr			10–24 yr			1–24 yr		
Type	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
All pancreatitis	106	5.0	4.1–6.1	80	2.5	2.0–3.1	44	1.5	1.1–2.0	230	2.8	2.5–3.2
Men	60	4.8	3.7–6.2	56	3.0	2.3–3.9	24	1.5	1.0–2.3	140	3.0	2.5–3.5
Women	46	5.4	3.9–7.2	24	1.8	1.2–2.7	20	1.5	0.9–2.3	90	2.6	2.1–3.1
One unspecified pancreatitis	5	12.7	4.1–29.6	4	7.5	2.0–19.3	1	2.2	0.0–12.5	10	7.3	3.5–13.4
Men	1	4.6	0.1–25.5	2	7.6	0.9–27.3	0	0.0	0.0–16.5	3	4.3	0.9–12.4
Women	4	22.8	6.1–58.3	2	7.5	0.8–27.0	1	4.5	0.1–24.9	7	10.5	4.2–21.6
One acute pancreatitis	35	2.4	1.6–3.3	34	1.6	1.1–2.2	22	1.2	0.7–1.7	91	1.6	1.3–2.0
Men	18	2.1	1.2–3.3	24	2.0	1.3–2.9	12	1.2	0.6–2.2	54	1.8	1.3–2.3
Women	17	2.7	1.6–4.3	10	1.1	0.5–2.0	10	1.0	0.5–1.9	37	1.5	1.0–2.0
Recurrent pancreatitis	20	5.3	3.3–8.2	26	4.2	2.7–6.1	13	2.2	1.2–3.7	59	3.7	2.8–4.8
Men	12	5.3	2.7–9.2	21	5.7	3.5–8.7	8	2.4	1.0–4.6	41	4.4	3.1–5.9
Women	8	5.5	2.3–10.8	5	2.0	0.6–4.6	5	2.0	0.6–4.6	18	2.7	1.6–4.3
Chronic pancreatitis	46	22.2	16.2–29.6	16	4.6	2.6–7.5	8	2.2	0.9–4.4	70	7.6	6.0–9.7
Men	29	20.3	13.6–29.2	9	3.8	1.7–7.2	4	1.6	0.4–4.2	42	6.7	4.9–9.1
Women	17	26.4	15.4–42.2	7	6.3	2.5–13.1	4	3.4	0.9–8.8	28	9.6	6.4–13.9
Pancreatitis associated with gallbladder disease	29	2.7	1.9–3.8	35	2.1	1.5–2.3	21	1.3	0.8–1.9	85	1.9	1.6–2.4
Men	9	1.6	0.7–3.0	23	2.7	1.7–4.1	7	0.9	0.4–1.9	39	1.8	1.3–2.5
Women	20	3.9	2.4–6.1	12	1.5	0.8–2.6	14	1.6	0.9–2.6	46	2.1	1.5–2.8
Alcoholism	4	3.2	0.8–8.1	4	2.0	0.5–5.0	7	3.8	1.5–7.9	15	2.9	1.6–4.8
Men	4	3.5	0.9–8.9	3	1.6	0.3–4.7	6	3.7	1.3–8.0	13	2.8	1.5–4.8
Women	0	0.0	0.0–35.9	1	5.4	0.1–30.0	1	5.4	0.1–30.0	2	4.2	0.5–15.2
Without any association with gallbladder disease or alcoholism	73	8.1	6.4–10.2	41	3.1	2.2–4.2	16	1.5	0.8–2.4	130	3.9	3.3–4.7
Men	47	8.4	6.2–11.2	30	3.7	2.5–5.2	11	1.6	0.8–2.9	88	4.3	3.4–5.2
Women	26	7.6	5.0–11.2	11	2.2	1.1–3.9	5	1.2	0.4–2.9	42	3.4	2.4–4.5

reported by Lowenfels et al.[10] Although patients with unspecified or chronic pancreatitis had a sevenfold increased risk, the excess was mainly confined to the early years and receded to twofold after a decade of follow-up. This finding is in accord with the results of Bansal et al.[13] but not with those reported by Lowenfels et al.[10]

Although Bansal et al.[13] did not find any differences in risk for pancreatitis patients with concurrent gallbladder disease or alcoholism, our analysis revealed a significant excess risk confined to patients with alcoholism, whereas no long-term increased risk was observed among patients with associated gallbladder disease (Table 3). The risk estimate in the group without recorded gallbladder disease or alcoholism was intermediate. Alcoholism is likely to be underreported in the Inpatient Register and may contribute to the modestly increased risk in this group of patients.

Smoking, an accepted risk factor for pancreatic cancer,[1,3–9] is likely to be more frequent among alcohol abusers.[21–23] Our finding of an increased risk for smoking-related cancers[24] among patients with alcoholism suggests that confounding by smoking may contribute to the association reported between pancreatitis and pancreatic cancer. Alcohol abuse per se may also influence the risk of pancreatic cancer, particulary in view of a recent case-control study suggesting that heavy alcohol intake may be a risk factor.[25]

Diabetes, which may develop as a consequence of chronic pancreatitis, is generally thought to be a risk

Table 4. Standardized Incidence Ratio for Respiratory Cancers by Years Since Pancreatitis Diagnosis and by Presence of Gallbladder Disease or Alcoholism

	1–4 yr			5–9 yr			10–24 yr			1–24 yr		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Respiratory cancer	67	1.3	1.1–1.6	126	1.6	1.3–1.9	101	1.4	1.2–1.7	294	1.5	1.3–1.6
Gallbladder disease	21	0.9	0.6–1.4	33	0.9	0.6–1.3	37	1.1	0.7–1.5	91	1.0	0.8–1.2
Alcoholism	13	2.8	1.5–4.7	28	3.6	2.4–5.2	14	2.1	1.1–3.5	55	2.9	2.2–3.7
Without any association of gallbladder disease or alcoholism	33	1.4	1.0–2.0	65	1.8	1.4–2.3	50	1.7	1.2–2.2	148	1.7	1.4–2.0

factor for pancreatic cancer. However, a recent meta-analysis of the association between diabetes and pancreatic cancer[2] revealed no instances in which diabetes was secondary to chronic pancreatitis.

In our study, there were substantially increased risks in the early years after a diagnosis of chronic, unspecified, or recurrent pancreatitis, with SIRs >20 among patients with chronic pancreatitis. Most, if not all, of the cancers occurring with short latency may have been present at entry into the cohort, and exclusion of cancers in the first year may not be sufficient to avoid selection bias. The temporal patterns of risk in our study suggest that chronic, unspecified, or recurrent pancreatitis may represent early manifestations of pancreatic cancer that is not clinically apparent until several years later. The risk estimates also decreased over time in the study by Bansal et al.[13] Similar findings have been reported for diabetes[2] and cholecystectomy,[26] with excesses of pancreatic cancer seen mainly in the first 5 years of follow-up. If pancreatitis were a cause rather than an effect of pancreatic cancer, it is of clinical interest that the absolute risk of pancreatic cancer in the first 4 years after a diagnosis of chronic pancreatitis in our study was one in 27.5.

The major strengths of our study are the prospective design, the large size and population-based nature of the cohort, and the long duration of follow-up. Moreover, the exclusion of patients diagnosed with a pancreatic cancer during the first year reduced, but did not eliminate selection bias. Although ascertainment or detection bias cannot be ruled out, it is unlikely to have had a major impact because most pancreatic cancers ultimately become clinically evident.

Limitations of the study must be noted, especially the uncertain validity of the pancreatitis diagnoses. However, patients with chronic or recurrent pancreatitis are less likely to be misclassified, and false-positive diagnoses are probably rare. Therefore, misclassification would not greatly influence our finding of a modest excess risk for pancreatic cancer. The problem of hidden alcoholism is obvious, because only heavy abuse would lead to a discharge diagnosis of alcoholism in the Inpatient Register. On the other hand, the specificity of a diagnosis of alcohol abuse is probably high as opposed to the sensitivity. The inclusion of patients with an unrecorded alcoholism may account, in part, for the slight excess risk among patients without a diagnosis of alcoholism or gallbladder disease. A final caveat is the screening effect by the work-up associated with the initial hospitalization. The screening would tend to uncover cases of cancer that would otherwise be detected later during the follow-up period, and may thus result in a spuriously low incidence over time. However, it is unlikely that the screening effect would persist after 10 years of follow-up. Furthermore, because of the recurrent nature of pancreatitis, the patients are likely to undergo repeated examinations that should enable early ascertainment of pancreatic cancer throughout the follow-up period, and thus counterbalance any delayed effect of initial screening.

In summary, the results of our cohort study do not provide strong support for a causal association between pancreatitis and pancreatic cancer. Selection bias, smoking habits, and possibly heavy alcohol use may have contributed to the elevated risks of pancreatic cancer reported after pancreatitis, but a slightly increased risk after chronic pancreatitis cannot be ruled out. Future large cohort studies with information about alcohol and tobacco use are needed to further clarify such an association.

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